



# **Regulatory Requirements for Verifying or Establishing Performance Specifications of Molecular Methods**

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# CLIA Law

CLIA applies to all facilities that perform:

*“examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings”*

CLIA is applicable to all clinical testing



# CLIA Regulations

- 1992 CLIA regulations included requirements for:
  - ❖ Patient test management
  - ❖ Quality control
  - ❖ Proficiency testing
  - ❖ Personnel
  - ❖ Quality assurance
- 2003 - Updated technical standards (re-designated quality system) and revised personnel qualification requirements for high complexity laboratory director



# Requirements for Verifying or Establishing Performance Specifications

- Applies to each nonwaived test system introduced on or after April 24, 2003
- Requirements pertain to
  - ❖ A test system introduced for the first time
    - o New analyte
    - o Analyte previously measured/detected on an alternate system
  - ❖ An analyte added to a test system
  - ❖ A modification to a test system



# Verifying Performance Specifications

- Applies to unmodified, FDA-cleared or approved test systems
- Laboratory must
  - ❖ Demonstrate it can obtain performance specifications comparable to the manufacturer before reporting patient results
    - o Accuracy
    - o Precision
    - o Reportable range of test results
  - ❖ Verify appropriate reference intervals (normal values) for the laboratory's population



# Establishing Performance Specifications

- Applies to
  - ❖ In-house methods
  - ❖ Modified commercial assays
  - ❖ Standardized (text book) procedures
  - ❖ Assays not subject to FDA clearance or approval [including those that incorporate analyte specific reagents (ASRs)]
- Before reporting patient results, the laboratory must establish
  - ❖ Accuracy
  - ❖ Precision
  - ❖ Reportable range
  - ❖ Analytical sensitivity
  - ❖ Analytic specificity
  - ❖ Reference intervals



# Verifying or Establishing Performance Specifications

- When multiple instruments or systems are used to perform the same test, the laboratory must verify or establish performance specifications for each instrument
- All activities for verifying or establishing performance must be documented
- Calibration procedures and control procedures must be based upon the verified or established performance specifications



# Assays for Agents of Emergent Public Health Significance

- Screening/confirmation of agents of emergent public health (PH) significance require rapid deployment of assays to PH laboratories for testing at the local level
- PH laboratories
  - ❖ May receive temporary exemption from CLIA requirements for establishing performance and control testing when reference or control materials are not available
  - ❖ Must follow assay protocols without modification and document alternative mechanisms for ensuring accurate results until materials are available, at which time all CLIA requirements must be met





# Assays for Agents of Emergent Public Health Significance

- Examples of alternative mechanisms
  - ❖ Test split samples by another method or laboratory
  - ❖ Test replicates of previously tested patients
  - ❖ Test patient samples in duplicate or multiple samples from the same patient
  - ❖ Confirm positive results using serial dilutions
  - ❖ Provide supervisory review of results
  - ❖ Use only trained personnel proficient in similar methods
- Specific instructions and testing information provided at [www.aphl.org](http://www.aphl.org)



# Analyte Specific Reagents

- FDA rule effective 11/23/98
- Describes ASRs as the "active ingredient of an in-house test"
- ASR rule impacts manufacturers and laboratories



# FDA Requirements for Laboratory Use of ASRs

- Be appropriately certified to conduct high complexity testing under CLIA
- Establish and maintain test performance under CLIA requirements
- Label test result to indicate status as in-house test as follows: *"This test was developed and its performance characteristics determined by [Lab name]. It has not been cleared or approved by the U.S. Food and Drug Administration."*



# CLIA Resources



- General information
  - ❖ <http://www.cms.hhs.gov/clia/>
  - ❖ <http://www.phppo.cdc.gov/clia/>
  - ❖ <http://www.fda.gov/cdrh/clia/index.html>
- Links to CLIA regulations and guidelines for compliance
  - ❖ Current CLIA regulations  
<http://www.phppo.cdc.gov/clia/regs/toc.aspx>
  - ❖ CMS interpretive guidelines for laboratories  
<http://www.cms.hhs.gov/clia/appendc.asp>
  - ❖ CLIA Brochure #2 - Verification of Performance Specifications  
<http://www.cms.hhs.gov/clia/6604bk.pdf>